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L6   ANSWER 1 OF 1  CA  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         132:302814  CA <<LOGINID::20060720>>
TITLE:                    Orally active peptidomimetic RGD analogs that are
                          glycoprotein IIb/IIIa antagonists
AUTHOR(S):                Wang, W.; Borchardt, R. T.; Wang, B.
CORPORATE SOURCE:         Department of Chemistry, North Carolina State
                          University, Raleigh, NC, 27695, USA
SOURCE:                   Current Medicinal Chemistry (2000), 7(4), 437-453
                          CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER:                Bentham Science Publishers
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review with 112 refs.  Peptidomimetic RGD (Arg-Gly-Asp) analogs, which
     bind to glycoprotein (GP) IIb/IIIa on the surface of activated platelets,
     have been shown to inhibit platelet aggregation.  Consequently, such RGD
     analogs can be used for the treatment of unstable angina pectoris and
     myocardial infarction.  However, the low oral bioavailability for this
     class of compds. has been hindering their clin. development.  Although
     many factors affect the oral activity of a drug, the limited membrane
     permeability of RGD analogs due to charge and high polarity is thought to
     be a major factor leading to the low oral activity of such compds.
     Another factor is the metabolic lability of some such RGD analogs in the
     presence of proteases and peptidases.  During the last 5 yr, major
     progress has been made in the development of orally active RGD analogs.
     To improve the metabolic stability of RGD analogs, N-alkylation and
     C-terminal modification methods have been used successfully.  To improve
     the membrane permeability of RGD analogs, two major strategies have been
     used.  The first one is the strategy of prodrug.  Along this line,
       ***simple***     ***ester***     ***prodrugs***  , double prodrugs, triple
     prodrugs, and cyclic prodrugs have been prepd. with improved membrane
     permeability and oral activity.  The second approach used is the de novo
     design of centrally constrained RGD analogs with improved oral
     bioavailability while maintaining the desired potency against GP IIb/IIIa.
     The lessons learned from the modification of RGD analogs could also help
     the future design of other peptidomimetic drugs with improved oral
     bioavailability.
REFERENCE COUNT:          77    THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


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L10  ANSWER 1 OF 1  USPATFULL on STN
ACCESSION NUMBER:         87:37989  USPATFULL <<LOGINID::20060720>>
TITLE:                    Substituted benzoate   ***ester***     ***prodrug***
                          derivatives of 3-hydroxymorphinans, which are
                            ***analgesics***   or narcotic antagonists
INVENTOR(S):              Shami, Elie G., Huntington, NY, United States
PATENT ASSIGNEE(S):       E.I. Du Pont de Nemours and Company, Wilmington, DE,
                          United States (U.S. corporation)

                               NUMBER        KIND    DATE
                          --------------- ------ --------
PATENT INFORMATION:       US 4668685              19870526            <--
APPLICATION INFO.:        US 1985-733464          19850514  (6)
RELATED APPLN. INFO.:     Continuation-in-part of Ser. No. US 1984-627923, filed
                          on 5 Jul 1984
DOCUMENT TYPE:            Utility
FILE SEGMENT:             Granted
PRIMARY EXAMINER:         Daus, Donald G.
ASSISTANT EXAMINER:       Rivers, Diana G.
NUMBER OF CLAIMS:         30
EXEMPLARY CLAIM:          1,11,21
LINE COUNT:               879
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Substituted benzoate ***ester*** ***prodrug*** derivatives of 3-hydroxymorphinans are useful as analgesics or narcotic antagonists and provide enhanced bioavailability of 3-hydroxymorphinans from orally administered doses.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L14 ANSWER 1 OF 4 USPATFULL on STN

ACCESSION NUMBER:	2001:102822 USPATFULL <<LOGINID::20060720>>
TITLE:	Acyclic nucleoside derivatives
INVENTOR(S):	Engelhardt, Per, Stockholm, Sweden Hogberg, Marita, Tullinge, Sweden Johansson, Nils-Gunnar, Enhorna, Sweden Zhou, Xiao-Xiong, Huddinge, Sweden Lindborg, Bjorn, Bjornlunda, Sweden
PATENT ASSIGNEE(S):	Medivir AB, Huddinge, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6255312	B1	20010703	<--
APPLICATION INFO.:	US 1998-146194		19980903 (9)	
RELATED APPLN. INFO.:	Division of Ser. No. US 1997-798216, filed on 10 Feb 1997, now patented, Pat. No. US 5869493			

	NUMBER	DATE
PRIORITY INFORMATION:	SE 1996-613	19960216
	SE 1996-614	19960216

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Travers, Russell
LEGAL REPRESENTATIVE:	Birch, Stewart, Kolasch & Birch, LLP
NUMBER OF CLAIMS:	21
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT:	2093

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds of the Formula I ##STR1##

where one of R.sub.1 and R.sub.2 is --C(O)CH(CH(CH.sub.3).sub.2)NH.sub.2 or --C(O)CH(CH(CH.sub.3)CH.sub.2 CH.sub.3)NH.sub.2 ;

the other of R.sub.1 and R.sub.2 is --C(.dbd.O)C.sub.3 -C.sub.21 saturated or monounsaturated, optionally substituted alkyl; and

R.sub.3 is OH or H;

and pharmaceutically acceptable salts thereof have utility as enhanced bioavailability antivirals against herpes and retroviral infections.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 2 OF 4 USPATFULL on STN

ACCESSION NUMBER:	2001:18622 USPATFULL <<LOGINID::20060720>>
TITLE:	Synthesis of acyclic nucleoside derivatives
INVENTOR(S):	Leanna, M. Robert, Grayslake, IL, United States Hannick, Steven M., Highland Park, IL, United States Rasmussen, Michael, Kenosha, WI, United States Tien, Jien-Heh J., Vernon Hills, IL, United States Bhagavatula, Lakshmi, Vernon Hills, IL, United States Singam, Pulla Reddy, Des Plaines, IL, United States Gates, Bradley D., Mount Prospect, IL, United States Kolaczkowski, Lawrence, Gurnee, IL, United States Patel, Ramesh R., Chicago, IL, United States Wayne, Greg, Vernon Hills, IL, United States Lannoye, Greg, Wildwood, IL, United States Zhang, Weijiang, Grayslake, IL, United States Tian, Zhenping, Grayslake, IL, United States Lukin, Kirill A., Mundelein, IL, United States

Narayanan, Bikshandarkoil A., Mundelein, IL, United States
Riley, David A., Kenosha, WI, United States
Morton, Howard, Gurnee, IL, United States
Chang, Sou-Jen, Prairie View, IL, United States
Curty, Cynthia B., Gurnee, IL, United States
Plata, Daniel, Wadsworth, IL, United States
Bellettini, John, Waukegan, IL, United States
Shelat, Bhadra, Lake Forest, IL, United States
Spitz, Tiffany, Highland Park, IL, United States
Yang, Cheng-Xi, Glenview, IL, United States

PATENT ASSIGNEE(S): Mediver AB, Huddinge, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6184376	B1	20010206	<--
APPLICATION INFO.:	US 1998-130214		19980806	(9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-20231, filed on 6 Feb 1998, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-37517P	19970210 (60)
	US 1997-55153P	19970808 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Berch, Mark L.
LEGAL REPRESENTATIVE: Svensson, Leonard R.Birch, Stewart, Kolasch & Birch, LLP
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1,5,8,22
LINE COUNT: 3554
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and novel intermediates of the formula: ##STR1##

wherein R.sub.6 and R.sub.7 are lower alkyl or benzyl or R.sub.6 and R.sub.7 taken together are --CH.sub.2 CH.sub.2 --, --CH.sub.2 CH.sub.2 CH.sub.2 -- or --CH.sub.2 CH.sub.2 CH.sub.2 CH.sub.2 CH.sub.2 --, R.sub.8 is C.sub.1 -C.sub.21 alkyl or a C.sub.2 -C.sub.21 monounsaturated alkenyl, which may optionally be substituted with substitution substituents independently selected from the group consisting of hydroxy, C.sub.1 -C.sub.6 alkyl, C.sub.1 -C.sub.6 alkoxy, C.sub.1 -C.sub.6 alkoxy C.sub.1 -C.sub.6 alkyl, C.sub.1 -C.sub.6 alkanoyl, amino, halo, cyano, azido, oxo, mercapto and nitro, and R.sub.9 is an alcohol protecting group. The intermediates are useful for the preparation of acyclic nucleoside derivatives of the formula: ##STR2##

where one of R.sub.1 and R.sub.2 is an amino acid acyl group and the other of R.sub.1 and R.sub.2 is a --C(O)C.sub.3 -C.sub.21 saturated or monounsaturated, optionally substituted alkyl and R.sub.3 is OH or H; or a pharmaceutically acceptable salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 3 OF 4 USPATFULL on STN
ACCESSION NUMBER: 1999:19157 USPATFULL <<LOGINID::20060720>>
TITLE: Acyclic nucleoside derivatives
INVENTOR(S): Engelhardt, Per, Stockholm, Sweden
Hogberg, Marita, Tullinge, Sweden
Johansson, Nils-Gunnar, Enhorna, Sweden
Zhou, Xiao-Xiong, Huddinge, Sweden
Lindborg, Bjorn, Bjornlunda, Sweden

PATENT ASSIGNEE(S): Medivir AB, Huddinge, Sweden (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5869493		19990209	<--
APPLICATION INFO.:	US 1997-798216		19970210	(8)

	NUMBER	DATE

PRIORITY INFORMATION: SE 1996-613 19960216
SE 1996-614 19960216
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Berch, Mark L.
LEGAL REPRESENTATIVE: Birch, Stewart, Kolasch & Birch, LLP
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 2029
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds of the Formula I ##STR1## where one of R.sub.1 and R.sub.2 is --C(O)CH(CH(CH.sub.3).sub.2)NH.sub.2 or --C(O)CH(CH(CH.sub.3)CH.sub.2 CH.sub.3)NH.sub.2;

the other of R.sub.1 and R.sub.2 is --C(.dbd.O)C.sub.3 -C.sub.21 saturated or monounsaturated, optionally substituted alkyl; and

R.sub.3 is OH or H;

and pharmaceutically acceptable salts thereof have utility as enhanced bioavailability antivirals against herpes and retroviral infections.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 4 OF 4 USPATFULL on STN
ACCESSION NUMBER: 1998:39732 USPATFULL <<LOGINID::20060720>>
TITLE: CC-1065 analogs
INVENTOR(S): Kelly, Robert C., Augusta, MI, United States
Mitchell, Mark A., Kalamazoo, MI, United States
Aristoff, Paul A., Kalamazoo, MI, United States
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, Kalamazoo, MI, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5739350		19980414	<--
APPLICATION INFO.:	US 1995-479231		19950607	(8)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-279767, filed on 25 Jul 1994, now abandoned which is a continuation of Ser. No. US 1992-966139, filed on 23 Oct 1992, now abandoned which is a continuation of Ser. No. US 1990-513501, filed on 25 Apr 1990, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Sripada, Pavanaram K.
LEGAL REPRESENTATIVE: Jameson, William G.
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 3071
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides some new synthetically obtained compounds of formula I and II ##STR1## which are useful as chemical intermediates. Representative formula I or II compounds have also been shown to possess useful ranges of antitumor activity in standard laboratory animal tests.

In addition, the compounds of formula I or II can be linked to monoclonal antibodies, either directly or via known linking group, as a means of selectively delivering the CC-1065 analogs (Compounds of Formula I and II) to those target cells expressing the target antigen and thus selectively eliminating those diseased cells from the animal or human. Further, the compounds of formula I and II can be linked to soluble human CD4 or a soluble human CD4 protein fragment capable of binding to the gp120 envelope protein of the human immuno-virus and thus eliminate virally infected cells.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d ibib abs 3 l17

L17 ANSWER 3 OF 11 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 126:271759 CA <<LOGINID::20060720>>
TITLE: Pharmacokinetics and metabolism of selected prodrugs of PMEA in rats
AUTHOR(S): Shaw, Jeng-Pyng; Louie, Michael S.; Krishnamurthy, V. V.; Arimilli, Murty N.; Jones, Robert J.; Bidgood, Alison M.; Lee, William A.; Cundy, Kenneth C.
CORPORATE SOURCE: Gilead Sciences, Inc., Foster City, CA, 94404, USA
SOURCE: Drug Metabolism and Disposition (***1997***), 25(3), 362-366
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The oral bioavailability of PMEA (9-[2-(phosphonomethoxy)ethyl]adenine; adefovir) has been detd. in rats from three bis- ***ester*** ***prodrugs*** of PMEA: bis-(pivaloyloxymethyl) PMEA (bis-POM PMEA), bis-(phenyl) PMEA, and bis-(o-ethoxyphenyl) PMEA. The prodrugs were each administered to 9 male rats as solns. in PEG 400 at a dose of 10 mg-equiv. of PMEA per kg. Plasma samples were obtained over the course of 12 h and concns. of PMEA were detd. by fluorescence derivatization and anal. by HPLC. Concns. of PMEA obsd. in plasma following oral administration of PMEA prodrugs were compared with levels obsd. for i.v. PMEA. The obsd. oral bioavailabilities of PMEA from bis-POM PMEA, bis-(phenyl) PMEA, and bis-(o-ethoxyphenyl) PMEA were 38.2%, 2.46%, and 40.1%, resp. PMEA was the only metabolite formed after oral administration of bis-POM PMEA. Three metabolites were detected after oral administration of either bis-(phenyl) PMEA or bis-(o-ethoxyphenyl) PMEA to rats: PMEA, the corresponding ***monoester*** , and 2-adenylacetic acid. The major metabolite of bis-(phenyl) PMEA was 2-adenylacetic acid following oral administration. 2-Adenylacetic acid appears to have been formed from the intact prodrugs by a P 450 mediated oxidn. of the Et side chain.

=> d l17 4-11 ibib abs

L17 ANSWER 4 OF 11 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 122:230590 CA <<LOGINID::20060720>>
TITLE: Prodrugs of valproic acid
AUTHOR(S): Bialer, Meir
CORPORATE SOURCE: School Pharmacy, Hebrew University Jerusalem, Jerusalem, 91120, Israel
SOURCE: Trends Med. Chem. '90, Proc. Int. Symp. Med. Chem., 11th (***1992***), 377-81. Editor(s): Sarel, Shalom; Mechoulam, Raphael; Agranat, Israel. Blackwell: Oxford, UK.
CODEN: 60TTAQ
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Valproic acid (VPA) is one of the major antiepileptic drugs. Because of its short half-life, VPA has to be administered several times a day, and there are fluctuations in VPA plasma levels during chronic treatment. An approach to overcome these problems is through the design of prodrugs, in which the biotransformation of the prodrug to the parent drug is used to obtain sustained plasma levels of the parent drug. Two types of VPA prodrugs, amide and ester, were studied and evaluated pharmacokinetically. The primary amide of VPA, valpromide (VPD), was a prodrug of VPA after oral and i.v. administration to humans. VPD is a solid, neutral, non-hygroscopic material, and as such it has several pharmaceutical advantages over VPA or sodium valproate. However, VPD has certain characteristics of its own, esp. in its interaction with carbamazepine. Three different ***monoester*** prodrugs of VPA were also studied by comparative pharmacokinetic anal. in dogs. This anal. included Et valproate, trichloroethyl valproate and valproyl valproate. The 3 ***ester*** ***prodrugs*** converted rapidly to VPA, and unlike VPD, they did not show sustained release performance in their VPA plasma profile. VPD was more potent as an anticonvulsant than VPA; however it was also more toxic, and therefore its protective index was similar to that of VPA. The different ***ester*** ***prodrugs*** showed less anticonvulsant activity than VPA. It seems that unlike the ***ester***

prodrugs , VPD may possess certain pharmaceutical and pharmacol. advantages over the parent drug, VPA.

L17 ANSWER 5 OF 11 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 118:182 CA <<LOGINID::20060720>>
TITLE: Pharmacokinetic analysis of ***ester*** ***prodrugs*** of valproic acid
AUTHOR(S): Hadad, Salim; Vree, Tom B.; Van der Kleijn, Eppo; Bialer, Meir
CORPORATE SOURCE: Sch. Pharm., Hebrew Univ., Jerusalem, Israel
SOURCE: Journal of Pharmaceutical Sciences (***1992***), 81(10), 1047-50
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacokinetics of five ***monoester*** prodrugs of valproic acid (VPA) were investigated: Pr valproate (P-VPA), Bu valproate (B-VPA), iso-Bu valproate (IB-VPA), isoamyl valproate (IA-VPA), and hexyl valproate (H-VPA). In addn., the anticonvulsant activity of these compds. was evaluated and compared with that of VPA and valpromide (VPD). The pharmacokinetics of VPA and its five ester derivs. were detd. after i.v. administration of equiv. doses (400 mg of VPA) to six dogs. The five ***ester*** ***prodrugs*** of VPA were biotransformed to VPA; the biotransformation was complete for P-VPA, B-VPA, and H-VPA but was only partial for IB-VPA and IA-VPA. Because of the rapid conversion of the prodrugs to the parent drug, levels of VPA in plasma after administration of the prodrugs peaked at 6-26 min after dosing and did not yield an in vivo sustained-release dosage profile. Of the five ***ester*** ***prodrugs*** of VPA, only P-VPA demonstrated anticonvulsant activity. P-VPA also was less neurotoxic than VPA and VPD; therefore, it has a better protective index.

L17 ANSWER 6 OF 11 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 116:27945 CA <<LOGINID::20060720>>
TITLE: O,O'-(1,4-Xylylene)bispilocarpic acid esters as new potential double prodrugs of pilocarpine for improved ocular delivery. II. Physicochemical properties, stability, solubility and enzymatic hydrolysis
AUTHOR(S): Jarvinen, Tomi; Suhonen, Pekka; Urtti, Arto; Peura, Pekka
CORPORATE SOURCE: Dep. Pharm. Chem., Univ. Kuopio, Kuopio, SF-70211, Finland
SOURCE: International Journal of Pharmaceutics (***1991***), 75(2-3), 259-69
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

/ Structure 1 in file .gra /

AB Various O,O'-(1,4-xylylene)pispilocarpic acid esters (I, R = alkyl, Ph, CH2CO2Me, or cyclopropyl) were evaluated as water-sol. double prodrugs of pilocarpine. All the prodrug derivs. (log P = 2.76-7.03) were more lipophilic than pilocarpine (log P = 0.01) as detd. from partitioning between 1-octanol and buffer (pH 7.40) or from liq. chromatog. capacity factors. The bispilocarpic acid diester fumarates were shown to be more water-sol. prodrugs than previously described pilocarpic acid diester fumarates. The aq. stability of the derivs. was investigated as a function of pH and temp. Maximal stability was achieved in acidic solns. The shelf-life of O,O'-dipropionyl (1,4-xylylene)bispilocarpate fumarate was 469 days at pH 6.0 and 4.degree.. Hence, the bispilocarpic acid diester prodrugs possess sufficient aq. stability to allow formulation of ready-to-use solns. The diesters were hydrolyzed enzymically to yield bispilocarpic acid ***monoester*** which cyclized to the parent pilocarpine in quant. amts. The half-lives of diesters in human plasma varied from 2 to 94 min, being highly dependent on the ester group. It appears that bispilocarpic acid diesters are a promising group of new pilocarpine prodrugs that offer possibilities from the results in stability, soly., lipophilicity, and enzymic hydrolysis tests.

L17 ANSWER 7 OF 11 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 113:217990 CA <<LOGINID::20060720>>
TITLE: Hydrolysis and acyl migration of a catechol ***monoester*** of L-dopa: L-3-(3-hydroxy-4-pivaloyloxyphenyl)alanine
AUTHOR(S): Ihara, Masaki; Nakajima, Shigeru; Hisaka, Akihiro; Tsuchiya, Yoshimi; Sakuma, Yumiko; Suzuki, Hiroko; Kitani, Koichi; Yano, Mitsuo
CORPORATE SOURCE: Cent. Res. Lab., Banyu Pharm. Co., Ltd., Tokyo, 153, Japan
SOURCE: Journal of Pharmaceutical Sciences (***1990***), 79(8), 703-8
CODEN: JPMSAE; ISSN: 0022-3549
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 113:217990
AB Hydrolysis and acyl migration in the title compd. (I, NB-355), which produced long-lasting plasma L-dopa levels after oral dosing, were studied. Compd. I exists as pure 4-O-pivaloyl-L-dopa in the solid state, but it converts rapidly to a mixt. of the 3- and 4-O-isomers in soln. The rate of acyl migration increased with increases in pH and temp., and the content of the 4-O-isomer in the equil. state was 53-59%. The hydrolysis rate of I to L-dopa also increased with increases in pH and temp., and accelerated steeply at neutral and alk. pH. The rapid hydrolysis at neutral pH was not obsd. with O-pivaloyl-L-tyrosine, di-O-pivaloyl-L-dopa, or L-dopa Me ester. Because of this chem. lability, I was hydrolyzed in rat plasma faster than the other tested catechol esters. However, in rat intestinal homogenate at pH 6.0, I was hydrolyzed at the slowest rate among the tested esters, predominantly by a diisofluorophosphate (DFP)-sensitive esterase. Thus, I showed a unique in vitro profile on hydrolysis and acyl migration due to existence of a neighboring hydroxyl group. The stability of I in the intestine might be essential for the long-lasting plasma L-dopa profile after oral dosing of I.

L17 ANSWER 8 OF 11 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 107:223142 CA <<LOGINID::20060720>>
TITLE: Ocular bioavailability of pilocarpic acid mono- and diester prodrugs as assessed by miotic activity in the rabbit
AUTHOR(S): Mosher, Gerold L.; Bundgaard, Hans; Falch, Erik; Larsen, Claus; Mikkelson, Thomas J.
CORPORATE SOURCE: Dep. Pharm. Chem., Univ. Kansas, Lawrence, KS, 66045, USA
SOURCE: International Journal of Pharmaceutics (***1987***), 39(1-2), 113-20
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Following topical ophthalmic dosing of rabbits with pilocarpic acid diester and ***monoester*** prodrug solns., significant biol. activity was obsd. The response, measured as pupillary diam., vs. time profiles, showed a slightly longer time requirement for attainment of maximal activity, a plateau region of sustained response, and a longer duration of action as compared to pilocarpine. Several monoesters were capable of maintaining durations of action 1.5-fold that of pilocarpine, while the diesters were active for up to 2.25-fold as long, and from half the dosing concn. The profile shapes eliminate the early spiking response seen with higher doses of pilocarpine. The bioavailability, as assessed by response, of the prodrugs relative to pilocarpine is a balance between 3 factors: prodrug lipophilicity, the kinetics of conversion from diester to ***monoester*** to pilocarpine, and ocular clearance or elimination rates. The increased bioavailability (response vs. time) of the diesters is primarily a result of their lipophilicity, with an optimum being seen. For the monoesters, the increase is dependent on the rate of the ***monoester*** to pilocarpine conversion. A linear correlation was established between the ***monoester*** structures and the activities obsd. following their dosing, through the use of the Taft .sigma. values for the alc. alkyl moieties. For the diesters, an inverted V-shaped correlation exists between the partition coeffs. of the prodrugs and their relative bioavailabilities, as calcd. from response data. In both cases, considerable predictability of response from prodrug structure should be

possible.

L17 ANSWER 9 OF 11 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 106:201633 CA <<LOGINID::20060720>>
TITLE: Physicochemical properties and chromatographic behavior of a homologous series of methotrexate-.alpha.,.gamma.-dialkyl ***ester*** ***prodrugs***
AUTHOR(S): Fort, James J.; Mitra, Ashim K.
CORPORATE SOURCE: Sch. Pharm., Purdue Univ., West Lafayette, IN, 47907, USA
SOURCE: International Journal of Pharmaceutics (***1987***), 36(1), 7-16
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

/ Structure 2 in file .gra /

AB A homologous series of 5 .alpha.,.gamma.-dialkyl ***ester*** ***prodrugs*** (I, R = Me, Et, Pr, Bu, pentyl) of methotrexate (I, R = H) [59-05-2] were synthesized by an acid-catalyzed direct esterification procedure. A HPLC method for sepg. each diester from its corresponding .alpha.- and .gamma.- ***monoester*** mixt. and methotrexate utilizing a pH 3 buffer soln./MeCN combination was developed. The physicochem. properties of each diester including their chromatog. capacity factors and octanol-DMF-water partition coeffs. were detd. as well as the correlation between these 2 parameters. The effect of chain length and mobile phase compn. on the capacity factors is shown. The methylene group contribution to both capacity factors and partition coeffs. were calcd. Also, the thermodn. significance of these findings, based on free energy calcns., is discussed. From the data obtained a discussion of the possible application of these compds. to the topical treatment of psoriasis is given.

L17 ANSWER 10 OF 11 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 103:42480 CA <<LOGINID::20060720>>
TITLE: Pilocarpic acid esters as novel sequentially labile pilocarpine prodrugs for improved ocular delivery
AUTHOR(S): Bundgaard, Hans; Falch, Erik; Larsen, Claus; Mosher, Gerold L.; Mikkelson, Thomas J.
CORPORATE SOURCE: Dep. Chem., R. Dan. Sch. Pharm., Copenhagen, DK-2100, Den.
SOURCE: Journal of Medicinal Chemistry (***1985***), 28(8), 979-81
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

/ Structure 3 in file .gra /

AB Various pilocarpic acid mono- (I, R = alkyl or PhCH2 or substituted benzyl) and diesters (II, R = PhCH2, 4-MeC6H4CH2, R1 = Ph or Pr) were synthesized and evaluated as prodrugs for pilocarpine [92-13-7]. The pilocarpic acid monoesters undergo a quant. cyclization to pilocarpine in aq. soln., the rate of cyclization being a function of the polar and steric effects within the alc. portion of the esters. At pH 7.4 and 37.degree., half-lives ranging from 30 to 1105 min were obsd. for the various esters. A main drawback of these monoesters is their poor soln. stability but this problem was overcome by esterification of the free hydroxy group. A no. of pilocarpic diesters so obtained were highly stable in aq. soln. and, most significantly, susceptible to undergo rapid enzymic hydrolysis at the O-acyl bond to give pilocarpine via the intermediate formation of pilocarpic acid ***monoester*** . Both the pilocarpic acid monoesters and, in particular, diesters afforded an enhanced ocular bioavailability of pilocarpine and a significantly

prolonged duration of pilocarpine activity following topical instillation as detd. by a miosis study in rabbits.

L17 ANSWER 11 OF 11 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 100:12587 CA <<LOGINID::20060720>>
TITLE: Pharmaceutical studies on the esterification of chloramphenicol with antipyretics. I
AUTHOR(S): Kim, Jung Woo; Kim, Jong Kap
CORPORATE SOURCE: Coll. Pharm., Chung Ang Univ., Seoul, 151, S. Korea
SOURCE: Yakhak Hoechi (***1983***), 27(3), 207-13
CODEN: YAHOA3; ISSN: 0513-4234
DOCUMENT TYPE: Journal
LANGUAGE: Korean
AB Chloramphenicol (I) [56-75-7] was esterified with aspirin [50-78-2], naproxen [22204-53-1] and acetaminophen succinic acid ***monoester*** [20675-25-6] to develop new prodrugs which have both antibiotic activity and antipyretic effect. I acetylsalicylate [88164-75-4], I naproxenate [88183-17-9], I acetaminophen succinate [88164-76-5] were prepd. using dicyclohexylcarbodiimide as the catalyst. The synthetic prodrugs did not show bitterness nor antibiotic activity in vitro, and were hydrolyzed in liver homogenate, but not by acids.

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	21.24	89.69

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-5.68	-10.65

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FILE 'CA' ENTERED AT 08:47:43 ON 20 JUL 2006
L1 792 S ESTER PRODRUG?
L2 614 S L1 AND PY<2002
L3 0 S ALKYL PRODRUG? AND L2
L4 4 S SIMPLE PRODRUG?
L5 0 S L4 AND L2
L6 1 S SIMPLE ESTER PRODRUG?

FILE 'STNGUIDE' ENTERED AT 08:49:13 ON 20 JUL 2006
L7 0 S L2 NOT L6

FILE 'CA' ENTERED AT 08:50:30 ON 20 JUL 2006
L8 613 S L2 NOT L6

FILE 'USPATFULL' ENTERED AT 08:50:47 ON 20 JUL 2006
L9 278 S L8
L10 1 S ANALGESICS/TI AND L9
L11 0 S AMPA RECEPTOR ANTAGONIS? AND L9
L12 654 S AMPA RECEPTOR
L13 0 S L12 AND L9
L14 4 S L9 AND(MONO ESTER)

FILE 'CA' ENTERED AT 08:56:23 ON 20 JUL 2006
L15 4068 S AMPA RECEPTOR?
L16 0 S L15 AND L8
L17 11 S L8 AND MONOESTER

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FILE 'CA' ENTERED AT 08:58:53 ON 20 JUL 2006

FILE 'STNGUIDE' ENTERED AT 08:59:33 ON 20 JUL 2006

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STN INTERNATIONAL LOGOFF AT 09:03:56 ON 20 JUL 2006